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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/791,155	03/01/2004	Amon Lavie	02-134-D	3822

7590 09/26/2005

Jason J. Derry
McDonnell Boehnen Hulbert & Berghoff LLP
300 S. Wacker Drive
Chicago, IL 60606

EXAMINER	
YAO, LEI	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 09/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/791,155	LAVIE ET AL.	
	Examiner	Art Unit	
	Lei Yao, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-169* is/are pending in the application.

4a) Of the above claim(s) *3,9,10,13-68 and 70-169* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4-8, 11-12 and 69* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *ID: AAE16385*.

SDO

DETAILED ACTION

Election/Restrictions

Applicant's election of Group I with specie SEQ ID NO: 5, leukemia, antibody for CD33, and AraC for nucleoside analog in the reply filed on 7/25/05 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1, 3, and 5 are amended. Claim 2 is canceled. Claims 1, and 3-169 are pending. Claims 3, 9-10, 13-68 and 70-169 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention. Claims 1, 4-8, 11-12 and 69 will be examined on the merits.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquires set forth in Graham V. john Deere Co., 383 U.S. 1, 148 USPQ 459 (1996), that are applied for establishing a background for determining obviousness under 25 U.S. C. 103 (a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or obviousness

1. Claims 1, 4-5, 11-12 and 69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bagshawe et al., (US Patent, 6299876, 2001) in view of Wolfgang et al., (WO 0188106, Nov, 2001).

The set of claims are drawn to an antibody-conjugated enzyme, wherein the antibody recognizes a cell surface antigen on the tumor cells and therein the enzyme is deoxycytidine kinase or modified deoxycytidine kinase, which activates a chemotherapeutic agent.

Bagshawe et al., teach an antibody- enzyme conjugate, which is used as combination chemotherapy (column 15, line 1-5). Bagshawe et al., teach that the antibody-enzyme conjugate generate a cytotoxic drug from an inactive precursor at tumor sited, which can prolong action of chemotherapeutic drug or increase the cytotoxicity of the drug (abstract and column 14, line 65-66). Bagshawe et al., also teach that the method is applied to anti-metabolite therapies, in which the enzyme in the conjugate could be for nucleoside synthesis and specifically inhibits the incorporation of nucleoside to the DNA in the tumor site since the antibody in the conjugate could bind to the surface of tumor cells (column 14, para 4). Bagshawe et al., also teach administering the antibody-enzyme conjugate comprising a pharmaceutical carrier to a patient (column 11, line 15-30).

Bagshawe et al., do not teach that the enzyme in the conjugate is wild type or modified deoxycytidine kinase.

Wolfgang et al., teach human deoxycytidine kinase (dCK) and modified dCK having nucleotide mutation as SEQ ID NO: 5 as evidenced by sequence search (ID AAE16385, see attached document). Wolfgang et al., teach that the modified dCK increases enzymatic activity towards nucleoside analogs, which is shown by the decrease of the lethal dose (LD_{100}) of a nucleoside analog (page 4, line, 3-7). Wolfgang et al., also show that the enzyme promotes the conversion of prodrug into a cytotoxic drug (page 4, line 17-20)

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to make enzyme-antibody conjugate of the primary reference comprising modified dCK of the secondary reference with the expected benefit for cancer treatment. One of ordinary skill in the art would have been motivated with a reasonable expectation of success to combine the teachings of Bagshawe et al., to the teaching of Wolfgang et al., to make the antibody-dCK enzyme conjugate comprising a modified dCK because Bagshawe et al., have shown a antibody-enzyme conjugate and

advantage of the conjugate in the cancer treatment and because Wolfgang et al., have shown human modified dCK that increases the activity to a nucleotide analog.

2. Claims 1, 4-8 and 11-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bagshawe et al., (US Patent, 6299876, 2001) and Wolfgang et al., (WO 0188106, Nov, 2001) and further in view of Kossman et al., (Clin Can Res. Vol. 5, Page 2748-55, 1999).

The set of claims are drawn to an antibody-conjugated enzyme, wherein the antibody is anti-CD33, HuM195, and therein the enzyme is deoxycytidine kinase or modified deoxycytidine kinase, which activates a chemotherapeutic agent.

The teachings of Bagshawe et al., and Wolfgang et al., are set forth above.

Both Bagshawe et al., and Wolfgang et al., do not teach that antibody in the conjugate is anti-CD33, HuM195 antibody, and tumor cell is leukemia blast cell.

Kossman et al., teach HuM195 antibody, which recognize CD33 antigen expressed on the myeloid leukemia cells (abstract and whole reference).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to make antibody, HuM195, conjugated with modified dCK of Bagshawe et al., Wolfgang et al., and Kossman et al., with the expected benefit for cancer treatment. One of ordinary skill in the art would have been motivated with a reasonable expectation of success to combine the teachings of Bagshawe et al., Wolfgang et al., and Kossman et al., to make the antibody-enzyme conjugate comprising a modified dCK and anti-CD33, HuM195 antibody conjugate because Bagshawe et al., have shown a antibody-enzyme conjugate, Wolfgang et al., have shown human modified dCK, which increases the activity to a nucleotide analog, and Kossman et al., have shown that HuM195 antibody targets CD33 on myeloid leukemia cells.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lei Yao, Ph.D. whose telephone number is 571-272-3112. The examiner can normally be reached on 8am-4.30pm Monday to Friday.

Any inquiry of a general nature, matching or file papers or relating to the status of this application or proceeding should be directed to Kim Downing for Art Unit 1642 whose telephone number is 571-272-0521

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lei Yao, Ph.D.
Examiner
Art Unit 1642

LY

SHEELA HUFF
PRIMARY EXAMINER

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RESULT 5
AAE16385
ID   AAE16385 standard; protein; 260 AA.
XX
AC   AAE16385;
XX
DT   26-MAR-2002  (first entry)
XX
DE   Human deoxycytidine kinase (hu-dCK) variant.
XX
KW   Multisubstrate deoxyribonucleotide kinase variant; nucleoside analogue;
KW   enzyme; cytotoxic; therapy; cancer; autoimmune disease; antibacterial;
KW   virucide; immunosuppressive; protozoacide; cytostatic; mutant; tumour;
KW   mutein; variant; human; deoxycytidine kinase; hu-dCK.
XX
OS   Homo sapiens.
XX
FH   Key             Location/Qualifiers
FT   Domain          28. .34
FT                   /note= "Motif 1"
FT   Domain          53. .58
FT                   /note= "Motif 2"
FT   Domain          127. .129
FT                   /note= "Motif 3"
FT   Domain          135. .136
FT                   /note= "Motif 4"
FT   Domain          188. .194
FT                   /note= "Motif 5"
FT
XX
PN   WO200188106-A2.
XX
PD   22-NOV-2001.
XX
PF   07-MAY-2001; 2001WO-DK000316.
XX
PR   12-MAY-2000; 2000DK-00000781.
XX
PA   (KNEC/) KNECHT W.
PA   (MUNC/) MUNCH-PETERSEN B.
PA   (PISK/) PISKUR J.
XX
PI   Knecht W,  Munch-Petersen B,  Piskur J;
XX
DR   WPI; 2002-097583/13.
XX
PT   New mutated nucleic acid encoding multisubstrate deoxyribonucleotide
PT   kinase, useful for sensitizing cells, e.g. tumors, against nucleoside
PT   analog prodrugs.
XX
PS   Claim 13; Page 8-9; 56pp; English.
XX
CC   The present invention relates to an isolated, mutated polynucleotide
CC   encoding a multisubstrate deoxyribonucleotide kinase. The mutated
CC   polynucleotide, when transferred into a bacterial or eukaryotic cell,
CC   reduces by at least 4 times the lethal dose (LD100) of at least one
CC   nucleoside analogue, compared to the wild-type enzyme. The mutated
CC   polynucleotide or vectors containing it are used to transform cells to
CC   render them sensitive to prodrugs, specifically nucleoside analogue which
CC   are converted to cytotoxic form by the multisubstrate deoxyribonucleotide
CC   kinase. The method is used to treat infections (viral, bacterial or
CC   protozoal); cancer, tumour and autoimmune diseases. Compared with wild-
CC   type enzymes, the multisubstrate deoxyribonucleotide kinase have higher
CC   catalytic efficiency for a wide variety of nucleoside analogue. The
CC   present sequence is human deoxycytidine kinase (hu-dCK) variant
XX
SQ   Sequence 260 AA;

  Query Match             98.8%;  Score 1370;  DB 5;  Length 260;
  Best Local Similarity   98.8%;  Pred. No. 2.2e-129;
  Matches  257;  Conservative    0;  Mismatches    3;  Indels    0;  Gaps    0;

Qy          1 MATPPKRSCPSFSASSEGTRIKKISIEGNIAAGKSTFVNILKQLCEDWEVVPEPVARWCN 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||

Db          1 MATPPKRSCPSFSASSEGTRIKKISIEGNIAAGKSTFVNILKQLCEDWEVVPEPVARWCN 60

Qy         61 VQSTQDEFEELTMSQKNGGNVLQMMYEKPERWSFTFQTYVCLSMIRAQLASLNGKLKDAE 120
              |||||||||||||||||||||||||||||||||||||||||||| ||| ||||||||||||||

Db         61 VQSTQDEFEELTMSQKNGGNVLQMMYEKPERWSFTFQTYACLSRIRAQLASLNGKLKDAE 120

Qy        121 KPVLFFERSVYSARYIFASNLYESECMNETEWTIYQDWHDWMNNQFGQSLELDGIIYLQA 180
              |||||||||||| ||||||||||||||||||||||||||||||||||||||||||||||||||

Db        121 KPVLFFERSVYSDRYIFASNLYESECMNETEWTIYQDWHDWMNNQFGQSLELDGIIYLQA 180

Qy        181 TPETCLHRIYLRGRNEEQGIPLEYLEKLHYKHESWLLHRTLKTNFDYLQEVPILTLDVNE 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||

Db        181 TPETCLHRIYLRGRNEEQGIPLEYLEKLHYKHESWLLHRTLKTNFDYLQEVPILTLDVNE 240

Qy        241 DFKDKYESLVEKVKEFLSTL 260
              ||||||||||||||||||||
Db        241 DFKDKYESLVEKVKEFLSTL 260


RESULT 6
AAO26449
ID   AAO26449 standard; protein; 260 AA.
XX
AC   AAO26449;
XX
DT   07-FEB-2003  (first entry)
XX
DE   Deoxycytidine kinase (DCK1) human protein wild-type.
XX
KW   Evolving; kinase; non-therapeutic; promutagenic analogue; mutagenesis;
KW   hypermutagenic process; 5'-phosphorylation; enzymatic phosphorylation;
KW   promutagen; gene therapy; deoxycytidine kinase; DCK1; enzyme; human;
KW   wild type.
XX
OS   Homo sapiens.
XX
PN   FR2823219-A1.
XX
PD   11-OCT-2002.
XX
PF   10-APR-2001; 2001FR-00004856.
XX
PR   10-APR-2001; 2001FR-00004856.
XX
PA   (INSP ) INST PASTEUR.
PA   (CNRS ) CNRS CENT NAT RECH SCI.
XX
PI   Marliere P,  Pochet S,  Bouzon M;
XX
DR   WPI; 2003-032224/03.
XX
PT   Process for evolving proteins, particularly kinases, useful e.g. in gene
PT   therapy, based on mutagenesis and testing for complementation of
PT   deficient, related enzymatic activity.
XX
PS   Disclosure; Page 9; 43pp; French.
XX
CC   The invention relates to a novel method for evolving a protein (X) to
CC   modify its properties. The method is especially used to generate a kinase
CC   that is used non-therapeutically: to activate a promutagenic analogue; in
CC   a hypermutagenic process; or to cause 5'-phosphorylation of nucleotides
CC   that are naturally refractory to enzymatic phosphorylation. When combined
CC   with other enzymes, kinases are used to broaden, in vivo, the range of
CC   mutagenesis by promutagens, and vectors (that include a kinase-encoding
CC   nucleic acid) are useful in gene therapy to allow the incorporation of
CC   nucleoside analogues into DNA. This sequence represents the deoxycytidine
CC   kinase DCK1 wild-type human protein of the invention
XX
SQ   Sequence 260 AA;

  Query Match             98.8%;  Score 1370;  DB 6;  Length 260;
  Best Local Similarity   98.8%;  Pred. No. 2.2e-129;
  Matches  257;  Conservative    0;  Mismatches    3;  Indels    0;  Gaps    0;
```